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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/802,516	03/17/2004	Stewart Loh	RFSUNY-3681 R1407	3967

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EXAMINER	
WHALEY, PABLO S	

ART UNIT	PAPER NUMBER
1631	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/802,516	LOH ET AL.	
	Examiner	Art Unit	
	Pablo Whaley	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6 and 8-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 8-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

REQUEST FOR CONTINUED EXAMINATION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 02/27/2007 has been entered.

CLAIMS UNDER EXAMINATION

Claims 1-6 and 8-11 are herein under examination. Claim 7 has been cancelled. Applicants' response, filed 02/27/2007, has been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied, as necessitated by amendment. They constitute the complete set presently being applied to the instant application.

OBJECTIONS

Applicant's amendment of the specification disclosure, specifically the "Detailed description of the invention" which now includes a description for element #25 as shown in Fig. 1B, is acceptable.

PRIORITY

Priority to US Provisional Application 60/456,965, filed 03/21/2003, has been acknowledged.

LACK OF UTILITY

Claims 1-6 and 8-11 were rejected under 35 U.S.C. 101 because the claimed invention was not supported by either an asserted utility or a well-established utility. Applicant's arguments, filed 02/27/2007, are persuasive in view of the amendment(s) to instant claim(s) 7 which not recites a fusion protein comprising a ubiquitin insert protein and a barnase target protein. This rejection is hereby withdrawn.

CLAIM REJECTIONS - 35 USC § 112, 2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-6 and 8-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 1-6 and 8-11 are rejected for the following reasons. Claims which are directly or indirectly dependent from claim(s) 1 are also included as rejected herein, due to said dependence.

Claim 1 recites the limitation "the...domain being associated with a....quantity of free energy" (line 3, line 7, and elsewhere). This limitation appears to be a method step. However, as the claimed invention is directed to a fusion protein, it is unclear whether applicant intends this limitation to be an active step, a further limitation of said domain, or something else. Clarification is requested via clearer claim language.

Claim 3 recites the limitation "wherein all or part of the...quantity of free energy is made available to drive a folding of the target...domain...". This limitation appears to be a method step. However, as the claimed invention is directed to a fusion protein, it is unclear whether this limitation is an intended use of said free energy, an active method step (e.g. folding), or a limitation of the fusion protein. If the latter, it is unclear in what way the above limitation further limits the claimed fusion protein. Clarification is requested via clearer claim language.

Claim 6 recites the limitation "wherein the insert domain and the target domain are disenabled from simultaneously coexisting". This limitation appears to be a method step. However, as the claimed invention is directed to a fusion protein, it is unclear whether this limitation is intended to be an active method step or a limitation of the fusion protein. If the latter, it is unclear in what way this limitation further limits the claimed fusion protein. Clarification is requested via clearer claim language.

Claim 8 recites the limitation "wherein any excess of the first quantity of free energy...is spontaneously transferred". This limitation appears to be a method step. However, as the claimed invention is directed to a fusion protein, it is in what way this limitation further limits the claimed fusion protein. Clarification is requested via clearer claim language.

Claim 9 recites the limitation "is spontaneously transferred". This limitation appears to be a method step. However, as the claimed invention is directed to a fusion protein, it is unclear in what way this limitation further limits the claimed fusion protein. Clarification is requested via clearer claim language.

Claim 11 recites the limitation "that may be determined by the....effector signals". This limitation appears to be a method step. However, as the claimed invention is directed to a fusion protein, it is unclear whether this limitation is an intended use, an active method step, or a

limitation of the fusion protein. If the latter, it is unclear in what way the above limitation further limits the claimed fusion protein. Clarification is requested via clearer claim language.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1 and 2 are rejected under 35 U.S.C. 103(a) as being made obvious by Doi et al. (FEBS Letters, 1999, Vol. 457, p.1-4), in view of Sevcik et al. (J. Biol. Chem., December 6, 2002 ,Vol. 277, Issue 49, p. 47325-47330), Hochstrasser (Nature Cell Biology, 2000, Vol. 2 , p.E153-E157), and Varshavsky (Proc. Natl. Acad. Sci., March 1998, Vol. 95, pp. 2094–2099).

Doi et al. teach methods for engineering insertional fusion proteins [Abstract] and [Table 1]. Doi et al. teach the insertion of a sequence of proteins (i.e. insert protein) into a surface loop region of an enzyme (i.e. target domain) domains [Section 2.2], wherein insertions are between N-terminal and C-terminals [Fig. 1 and 2], as in claim 1. Doi et al. also teach the design of biosensor proteins, wherein the activity of an insert domain is modulated by a conformational

change of a target domain [Section 2.3, Col. 1], and wherein proteins with desired molecular recognition domains (i.e. regulatory domains) are inserted into a target protein loop [Section 2.3, Col. 2, ¶ 2], as in claim 1. Doi et al. also teach insert domains and parent domains wherein insert domains are over twice the length of parent domains [Fig. 1] and [Table 1], as in claim 1. Doi et al. also teach insert proteins that switch between folded and unfolded conformations and are associated with high and low activity (i.e. energy) [Fig. 2], as in claim 2.

Doi et al. do not specifically teach fusion proteins comprising ubiquitin and barnase, as in claim 1. However, Doi et al. teach the use of Rnase (ribonuclease) as a parent domain (i.e. target protein), which suggests the use of proteins in the family of ribonucleases (e.g. barnase) [Fig. 2]. Doi et al. also suggest this technique should be used for designing stable bifunctional proteins [p.3, Col. 2, ¶ 1].

Sevcik et al. teach the cytotoxic ribonuclease protein *barnase* in complex with barstar for use in treating cancer [p.47325, Col. 2], and provides evidence that the conformational stability of barnase correlates with toxicity [p.47329, Col. 1, ¶ 5].

Hochstrasser teaches ubiquitin (and ubiquitin-related proteins) as the prototypical example of a regulatory stratagem for covalently modifying another protein, thereby altering its physiological properties [p. E153, Col. 1, ¶ 1 and 2], because ubiquitin advantageously possesses a larger and more chemically varied surface area [p. E153, Col. 1, ¶ 2]. Hochstrasser also teaches ubiquitin attached to activating and conjugating enzymes (i.e. ubiquitination) [Fig. 2], and that attached ubiquitin modules can function as reversible connectors and could also link upstream synthetase to proteins or other molecules that regulate activity or localization of the enzyme [E156, Col. 1, ¶ 1].

Varshavsky teaches that with cancer, cytotoxic therapies generally fail due to their lack of selectivity [p.2094, Col. 1, ¶ 2] and their inability to adjust to intracellular protein levels

[p.2094, Col. 2, ¶ 2]. In response to this need, Varshavsky teaches that conditionally specific cytotoxic regimens must possess a multi-target combinatorial (positive/negative) selectivity [p.2095, Col. 1, ¶ 4 and 5] and introduces the concept of codominance interference [p.2095, Col. 2] wherein two signals in the same molecule function without interference in a mutually exclusive fashion to increase or decrease toxicity of the complex [Fig. 2] and [Fig. 4].

Thus it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to create a mutually exclusive fusion protein using the methods of Doi et al. and Varshavsky that contains barnase, as taught by Sevcik et al., and ubiquitin as taught by Hochstrasser, where the motivation would have been to design a drug that possesses qualitatively different selectivity [Varshavsky, p.2099, Col. 2], and where the incorporation of ubiquitin would have provided a well-known tool for regulating the function of barnase by covalent modification and additionally by linking it to other molecules that could regulate its activity [Hochstrasser], resulting in the practice of the instant claimed invention. One of skill in the art would have had a reasonable expectation of successfully combining the above teachings as Doi et al., Sevcik et al., and Hochstrasser all teach fusion proteins, and as Hochstrasser and Varshavsky both teach regulatory proteins. Furthermore, Hochstrasser teaches the fusion of ubiquitin with ribosomal proteins [p.E157, Col. 1, ¶ 1].

Claims 1-6 are rejected under 35 U.S.C. 103(a) as being made obvious by Doi et al., in view of Sevcik et al., Hochstrasser, and Varshavsky, as applied to claims 1 and 2 above, and further in view of Pace et al. (Biochemistry, 1992, Vol. 31, p. 2728-2734) and Wintrode et al. (PROTEINS: Structure, Function, and Genetics, 1994, p.18246-253).

Doi et al., Sevcik et al., Hochstrasser, and Varshavsky make obvious a fusion protein as in claims 1 and 2, as set forth above.

Doi et al., Sevcik et al., Hochstrasser, and Varshavsky do not specifically teach limitations of claims 3, 4, and 5. However, Falnes et al. also teach the inactivity of surface-bound toxins by exposure to low pH [p.615, Col. 2, ¶ 2], as well as *in vivo* degradation signals used to reduce the toxicity of a protein toxin [p.620, Col. 1, ¶ 2] and [p.621, Col. 1, ¶ 2], which suggests disenabling proteins, as in claim 6, and controllable effector signals as in claims 3-5.

Pace et al. teach urea denaturation of barnase based on pH dependence [Abstract]. Pace et al. also teach that barnase stability is controllable by pH; barnase has a maximum conformational stability at higher pH values (i.e. 5-6) [p.2733, Col. 2, ¶ 5]; and barnase accessibility in both folded and unfolded conformations [Table II], as in claims 3-5.

Wintrode et al. teach thermodynamics of ubiquitin folding [Abstract]. More specifically, Wintrode et al. teach that ubiquitin is controllable by pH and is more stable at lower pH values [p.247, Col. 1, Results and Discussion]. Wintrode et al. also teach denaturation (i.e. folding) of ubiquitin is reversible and temperature dependent [p.247, Col. 2], and the folding/unfolding associated with energy quantities [Table IV], as in claims 3-5

Thus it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to create a mutually exclusive fusion protein using the methods of Doi et al. and Varshavsky that contains barnase, as taught by Sevcik et al., and ubiquitin as taught by Hochstrasser, and additionally using pH to control the cooperative folding of the barnase and ubiquitin, as taught by Wintrode et al. and Pace et al., as in claims 2-6, wherein the motivation would have been to determine optimal pH and temperature values for controlling barnase-ubiquitin fusion protein toxicity, the resulting in the practice of the instant claimed invention. One

of skill in the art would have had a reasonable expectation of successfully combining the above teachings as both Pace et al. and Wintrode et al. teach effects of pH on protein folding.

Provisional Obviousness-Type Double Patenting Rejection

The non-statutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 C.F.R. 1.321 (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R. 1.130(b). Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 C.F.R. 3.73(b).

Claims 1-6 and 8-11 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 of co-pending Application No. 11/670,966. Although the conflicting claims are not identical, they are not patentably distinct from each other because of the broadly encompassing scope of the instantly claimed invention causing the inventions to have overlapping embodiments. The instant claims and those of '966 recite the same method steps, with minor variations. For example, Claim 1 of the instant application recites "a fusion protein" limited to barnase and ubiquitin, whereas claim

1 of co-pending Application '966 is directed to a fusion protein comprising a target protein and insert protein. It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to practice the invention of '966 as barnase and ubiquitin are clearly species of target and insert proteins. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

CONCLUSION

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Pablo Whaley whose telephone number is (571)272-4425. The examiner can normally be reached on 9:30am - 6pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Pablo S. Whaley

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